FIGURE 1

Figure 2

START

RECEIVE MOLECULAR STRUCTURE — 303

GENERATE STANDARD 3D REP. — 305

OPTIMIZE 3D STRUCTURE USING AM1 — 307

301

IDENTIFY METABOLISM SITES — 309

N = # of METABOLISM SITES — 311

i = 1
i = i + 1   i > N? — 313   Yes → SEE FIGURE 3B

No

IS IT AN H+ ABST. SITE OR AROMATIC C? — 315   AROM. → ADD METHOXY GROUP — 319

H+

ABSTRACT H ATOM — 317

DETERMINE Ea BY AM1 SUBTRACTION — 323

DO AM1 CALCULATION ON RADICAL — 321

FIGURE 3A

SEE
FIGURE
3A

OUTPUT
REGIOSELECT-
IVITY TABLE   325

MAP Ea's TO
RELATIVE
RATES CURVE   327

OUTPUT
BINNED
LABILITY
SCORES FOR
ACTIVE SITES   329

CORRECT FOR
ACCESSIBILITY
FACTORS   331

DONE

FIGURE 3B

FIGURE 3C

LOVASTATIN Regioselectivity/Output Table		
site #	Ea	Lability Bin
1	6.71	labile
2	7.129	labile
3	8.944	moderate
4	9.502	moderate
5	9.806	moderate
6	10.396	moderate
7	10.515	stable
8	10.715	stable
9	10.856	stable
10	10.995	stable
11	11.02	stable
12	11.061	stable
13	11.097	stable
14	11.375	stable
15	11.401	stable
16	11.583	stable
17	11.599	stable
18	11.599	stable
water	10	NA

FIGURE 3D

FIGURE 3E

```
                    ┌─────────┐
                    │  START  │
                    └────┬────┘
                         │
                         ▼
              ┌──────────────────┐    403
              │   RECEIVE QM     │
              │   DATA FOR       │
              │   SUBSTRATE      │
              │   MOLECULE       │
              └────────┬─────────┘
                       │
                       ▼
              ┌──────────────────┐    405
              │   GENERATE       │
              │   SURFACE AREA   │
              │   CORRECTION     │
              └────────┬─────────┘
                       │
                       ▼
              ┌──────────────────┐    407
              │   GENERATE       │
              │   PARABOLIC      │
              │   CURVATURE      │
              │   CORRECTION     │
              └────────┬─────────┘
                       │
                       ▼
              ┌──────────────────┐    409
              │   GENERATE       │
              │   PROTRUSION     │
              │   CORRECTION     │
              └────────┬─────────┘
                       │
                       ▼
              ┌──────────────────┐    411
              │   GENERATE       │
              │   AMPHOTERIC     │
              │   CORRECTION     │
              └────────┬─────────┘
                       │
                       ▼
              ┌──────────────────┐    413
              │  GENERATE NEW    │
              │       EA         │
              └────────┬─────────┘
                       │
                       ▼
                  ┌─────────┐
                  │  DONE   │
                  └─────────┘
```

401

FIGURE 4

START

CHOOSE PROBE
RADIUS — 503

501

ALKYL or
AROMATIC
SITE? — 505

AROM. → DETERMINE C
SURFACE
ACCESSIBILITY — 507

ALKYL ↓

DETERMINE H
SURFACE
ACCESSIBILITY — 509

COMPARE TO
REFERENCE
STATE — 511

GENERATE K_P — 513

DONE
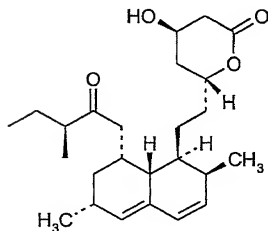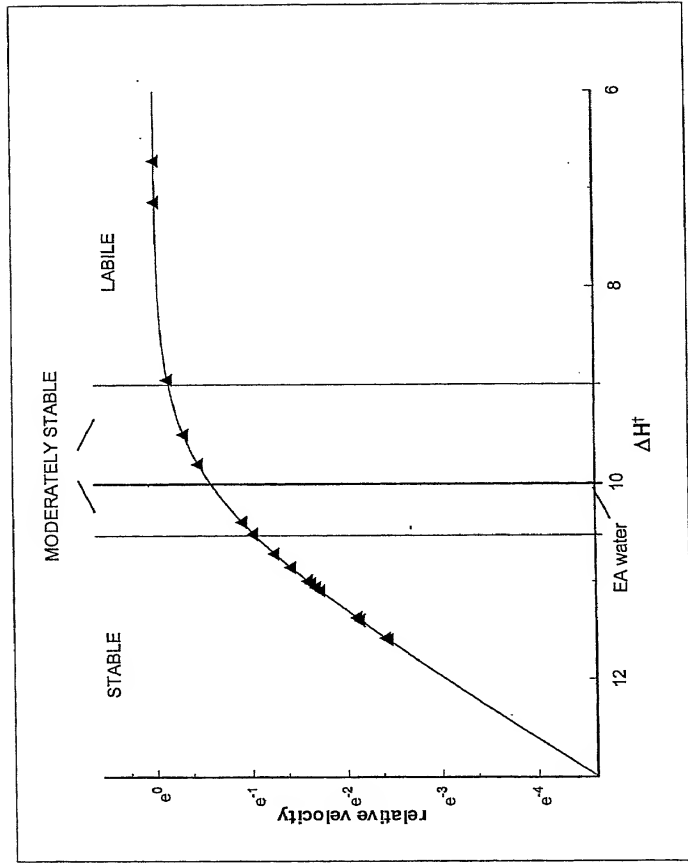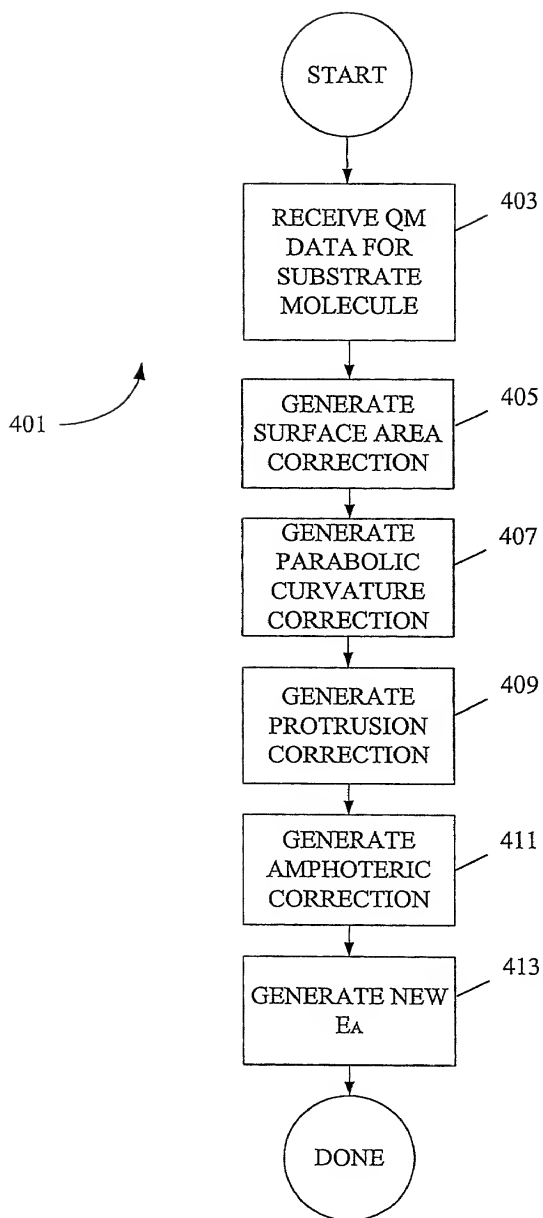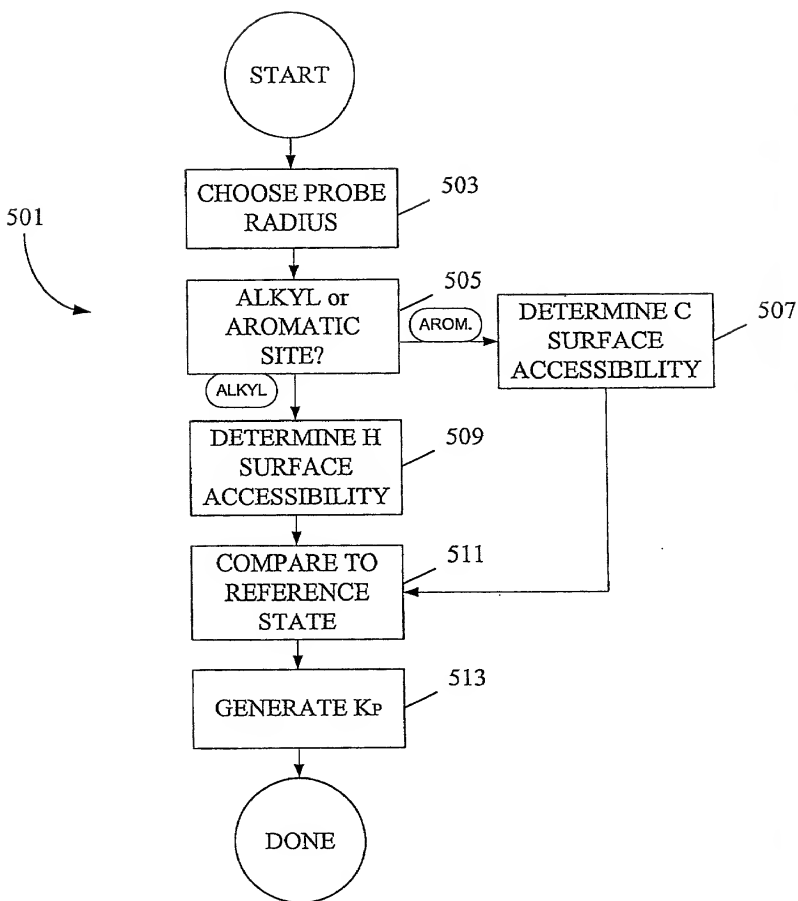
SURFACE AREA CORRECTION
$$K_{Sa} = X_{Sa}\, f(S(r))$$

FIGURE 5

```
                    ┌─────────────────┐
                    │   DETERMINE     │ ── 603
  ┌─────────┐       │ NUMBER OF CH    │
  │  START  │ ───▶  │   AXES AT       │
  └─────────┘       │ REACTIVE SITE   │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │ ASSIGN ORIGIN   │ ── 605
                    │ AND AXIS FOR    │
                    │   PARABOLA      │
   601 ──           └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │ FIT PARABOLAS   │ ── 607
                    │   TO ATOMS      │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │   GENERATE      │ ── 609
                    │  CURVATURE      │
                    │    VALUE        │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │ REPEAT 605-609  │ ── 611
                    │ FOR EACH AXIS   │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │   GENERATE      │ ── 613
                    │   OVERALL       │
                    │  CURVATURE      │
                    │    VALUE        │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │ REPEAT 611 and  │ ── 615
                    │ 613 FOR OTHER   │
                    │  CONFORMA-      │
                    │    TIONS        │
                    └─────────────────┘
                            │
                            ▼
                    ┌─────────────────┐
                    │   GENERATE      │ ── 617    ┌─────────┐
                    │   OVERALL       │ ───────▶  │  DONE   │
                    │  CURVATURE      │           └─────────┘
                    │    VALUE        │
                    └─────────────────┘
```
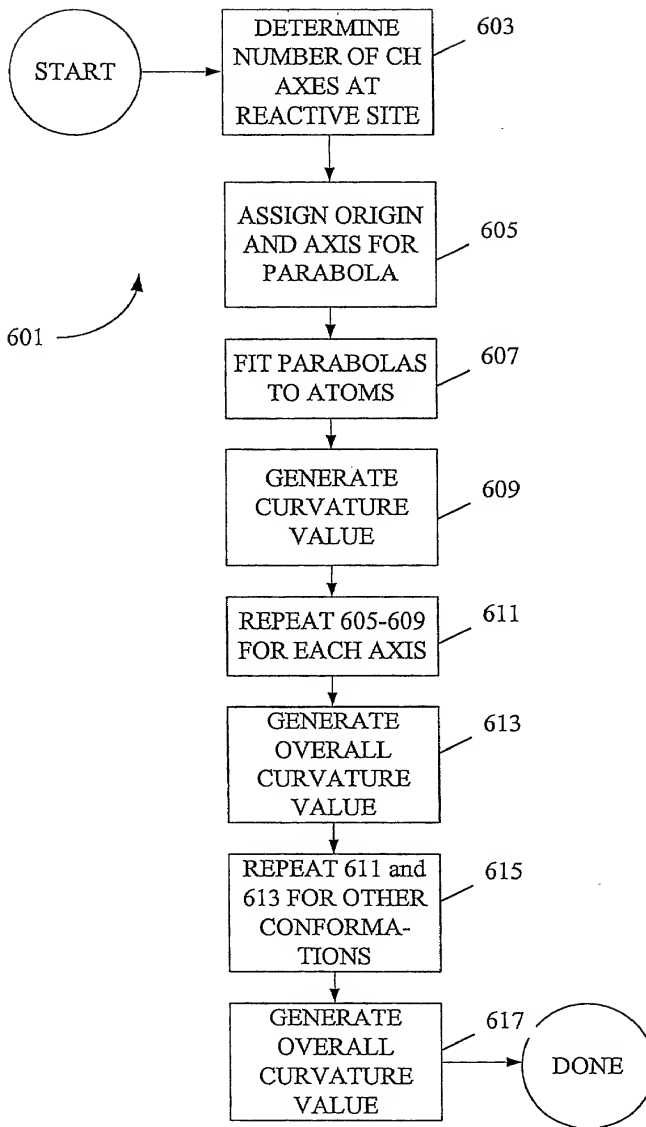
PARABOLIC CURVATURE
CORRECTION

$K_P = X_G P_G + X_S P_S + X_L P_L$

FIGURE 6A

657 659 653 655 651

Y

X

Cl

Cl

651

triazolam

FIGURE 6B

START

DRAW VECTOR TO REACTIVE CARBON — 703

ADD VAN DER WAALS RADIUS — 705

N = # of ATOMS — 707

701

i = 1
i = i + 1   i > N? — 709

Yes

No

GENERATE PROTRUSION CORRECTION — 717

DRAW VECTOR TO ATOM — 711

REPEAT 709-717 FOR OTHER CONFORM-ATIONS — 719

DETERMINE COMPONENT ALONG REACTION VECTOR — 713

GENERATE K_R

ADD VAN DER WAALS RADIUS — 715

DONE
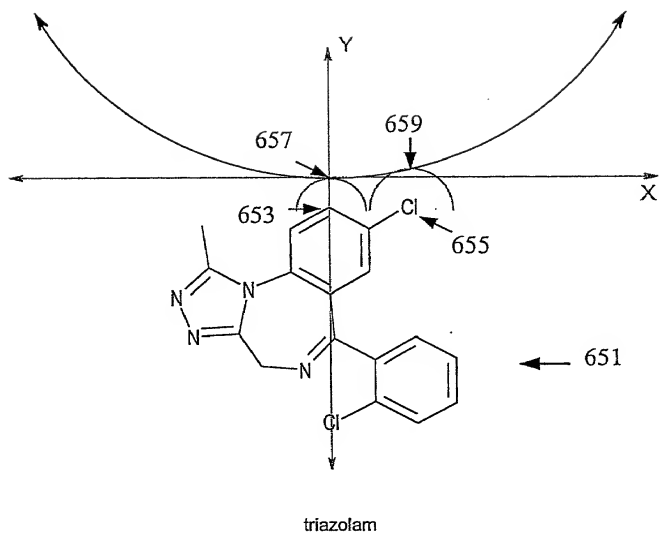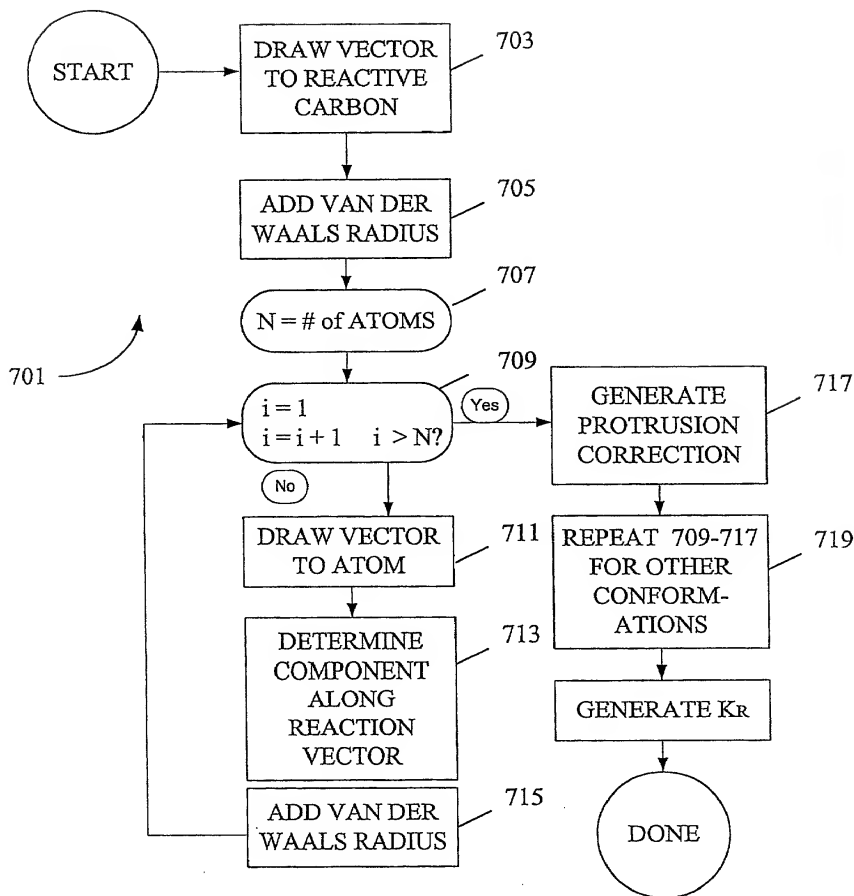
PROTRUSION CORRECTION

$$K_R = Y_G R_G + Y_S R_S + Y_L R_L$$

FIGURE 7A

FIGURE 7B

```
                         ┌─────────┐
                         │  START  │
                         └────┬────┘
                              │
                    ┌─────────▼─────────┐        803
                    │  N = # of ATOMS   │
                    └─────────┬─────────┘
                              │                  805
          ┌──────────┌────────▼────────┐  Yes  ┌──────────────┐      813
          │          │ i = 1           ├──────►│ DRAW VECTOR  │
          │          │ i = i + 1  i>N? │       │ TO REACTIVE  │
          │          └────────┬────────┘       │    SITE      │
          │               No  │                └──────┬───────┘
          │          ┌────────▼────────┐  807          │
          │          │  DRAW VECTOR    │       ┌───────▼───────┐    815
          │          │   TO ATOM       │       │  TAKE DOT     │
          │          └────────┬────────┘       │ PRODUCT WITH  │
          │          ┌────────▼────────┐  809   │  MOMENT       │
          │          │ DETERMINE       │       └───────┬───────┘
          │          │ PARTIAL         │               │
          │          │ CHARGE AND      │       ┌───────▼───────┐    817
          │          │ ACCESSIBLE      │       │  GENERATE Ka  │
          │          │ SURFACE         │       └───────┬───────┘
          │          └────────┬────────┘               │
          │          ┌────────▼────────┐  811    ┌─────▼─────┐
          └──────────┤ CALCULATE       │         │   DONE    │
                     │ AMPHOTERIC      │         └───────────┘
                     │ MOMENT          │
                     └─────────────────┘
```
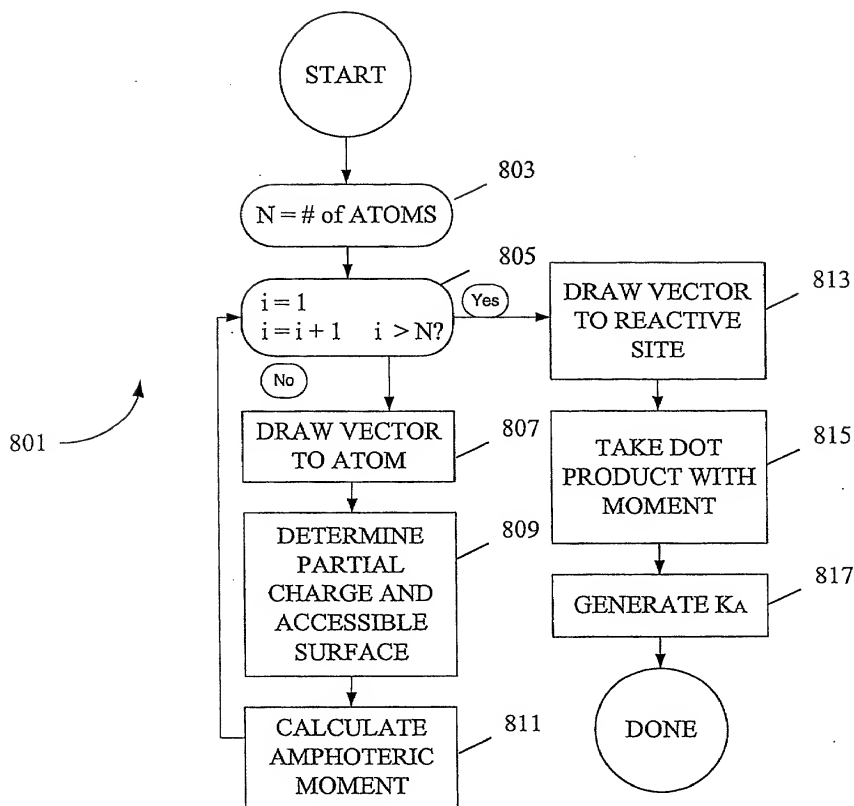
801
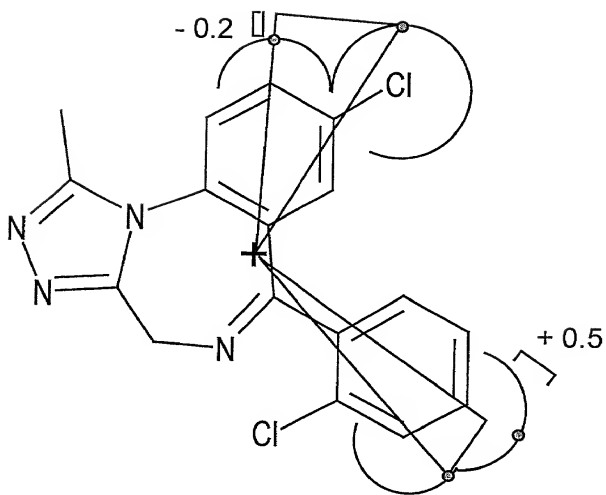
AMPHOTERIC CORRECTION

FIGURE 8

900

```
┌─────────────────┐
│   GENERATE q    │
│   AND S FOR     │ ── 901
│ EACH ATOM OF    │
│      THE        │
│   SUBSTRATE     │
└─────────────────┘
         │
         ▼
┌─────────────────┐
│   GENERATE p    │ ── 903
│   FOR EACH      │
│  ATOM OF THE    │
│   SUBSTRATE     │
└─────────────────┘
         │
         ▼
┌─────────────────┐
│                 │ ── 905
│   GENERATE      │
│  ORIENTATION    │
│    ACCESS       │
│  DESCRIPTORS    │
│   FOR EACH      │
│ REACTIVE SITE   │
└─────────────────┘
         │
         ▼
┌──────────────────────┐
│ REPEAT 905 FOR EACH  │
│  CONFORMATION AND    │
│ SELECT DESCRIPTOR SET│ ── 907
│    FROM AMONG        │
│  DESCRIPTORS OF      │
│    VARIOUS           │
│  CONFORMATIONS       │
└──────────────────────┘
```

FIGURE 9

FIG 10

1110

1100

1120

1140

FIG 11

```
GENERATE
STERIC ACCESS
DESCRIPTORS          1201
FOR EACH
REACTIVE SITE
```

```
REPEAT 1201          1203
FOR EACH
CONFORMATION
```

```
SELECT DESCRIPTOR SET    1205
FROM AMONG
DESCRIPTORS OF
VARIOUS
CONFORMATIONS
```
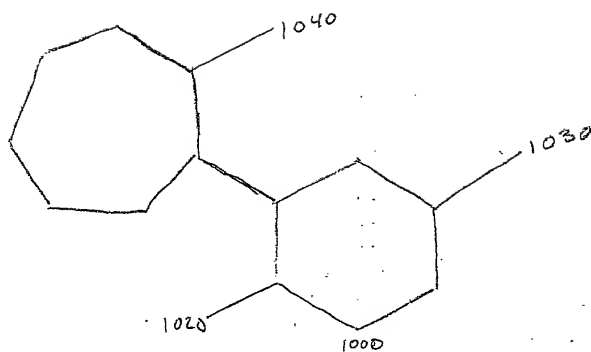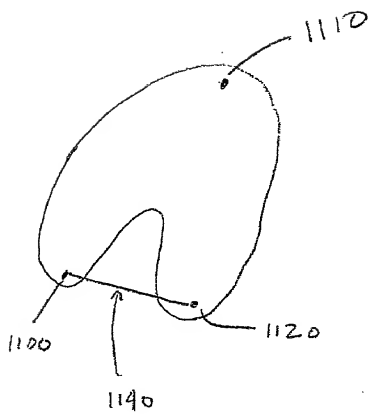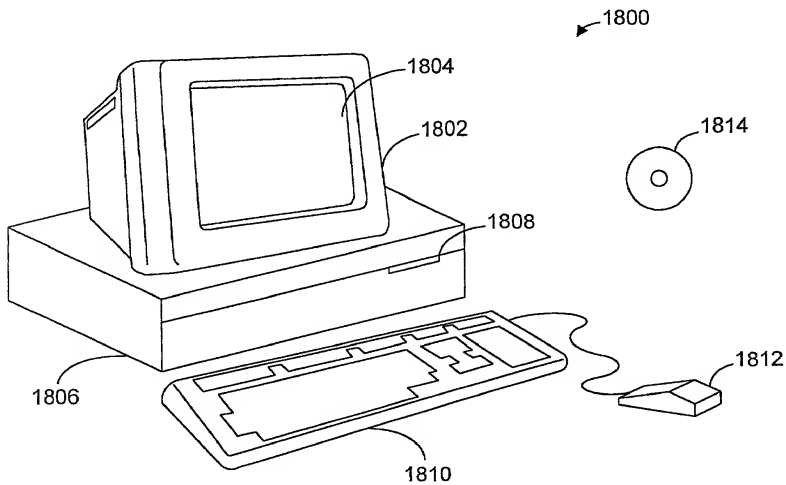
1200
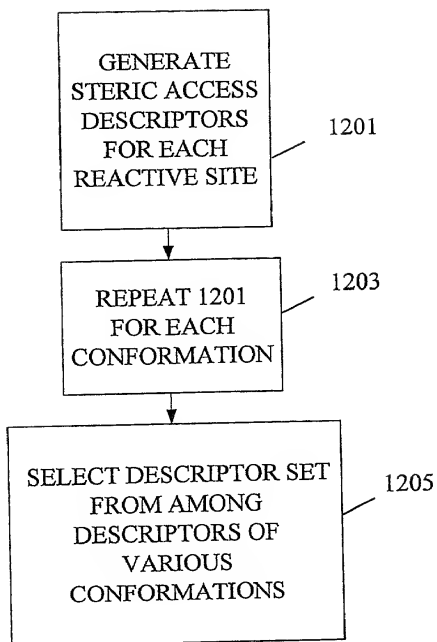
FIGURE 12

FIGURE 13

FIGURE 14

$$ X \quad c \quad = \quad y $$

Atoms
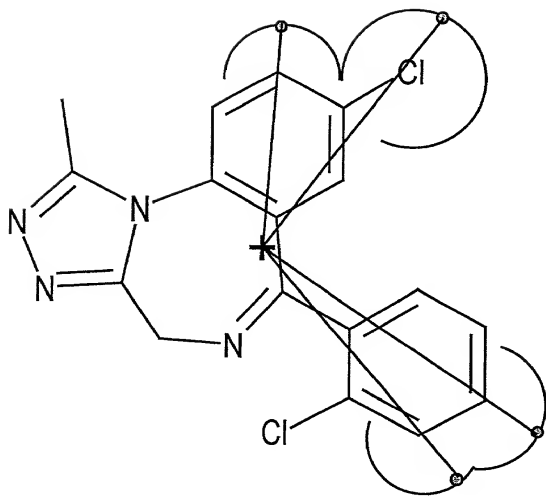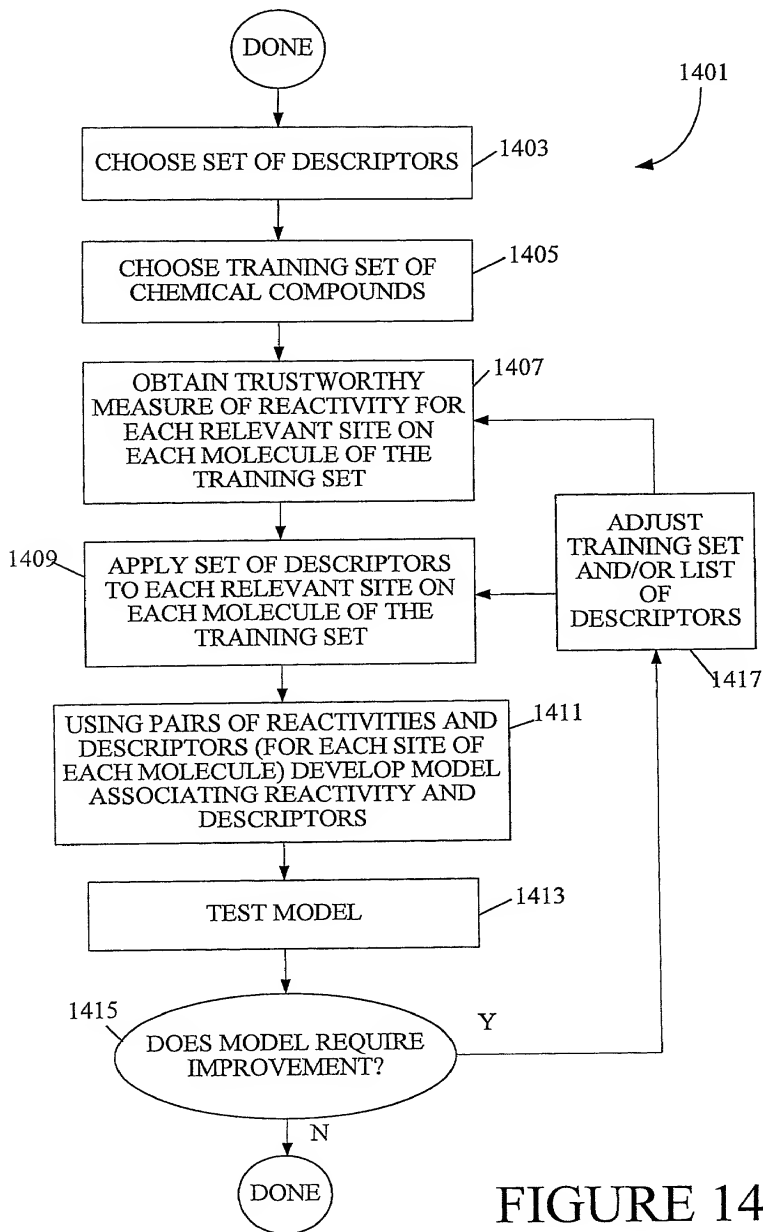
Descriptors   Coefficients   Activity

FIGURE 15

16
16A

FOR EACH TYPE OF
DESCRIPTOR, SET
THE ONE CORRESPONDING
TO MOST REACTIVE/
ACCESSIBLE TO ZERO
1601

MAKE EACH
DESCRIPTOR
RELATIVE TO THE
LOWEST OF ITS
TYPE
1602

ADJUST TRAINING
SET DATA
1603

PLS REGRESSION
1604

DIVIDE COEFFICIENTS
BY E_{HO}
1605

16B

SCALE
OF
E_{HO}
1606

INCREASE IMPORTANCE
OF METABOLIZED
SITES
1607

INCREASE
IMPORTANCE
OF UNDERSAMPLED
MECHANISMS
1608
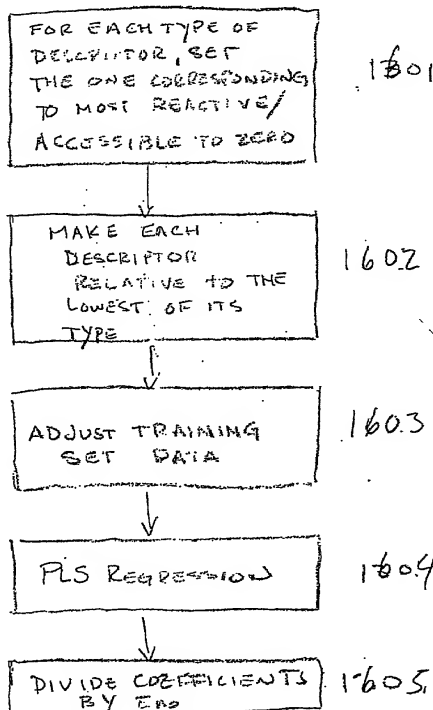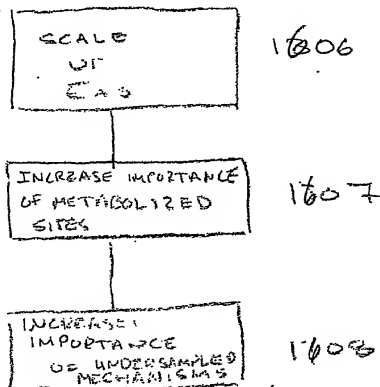
FIG 16 (   )
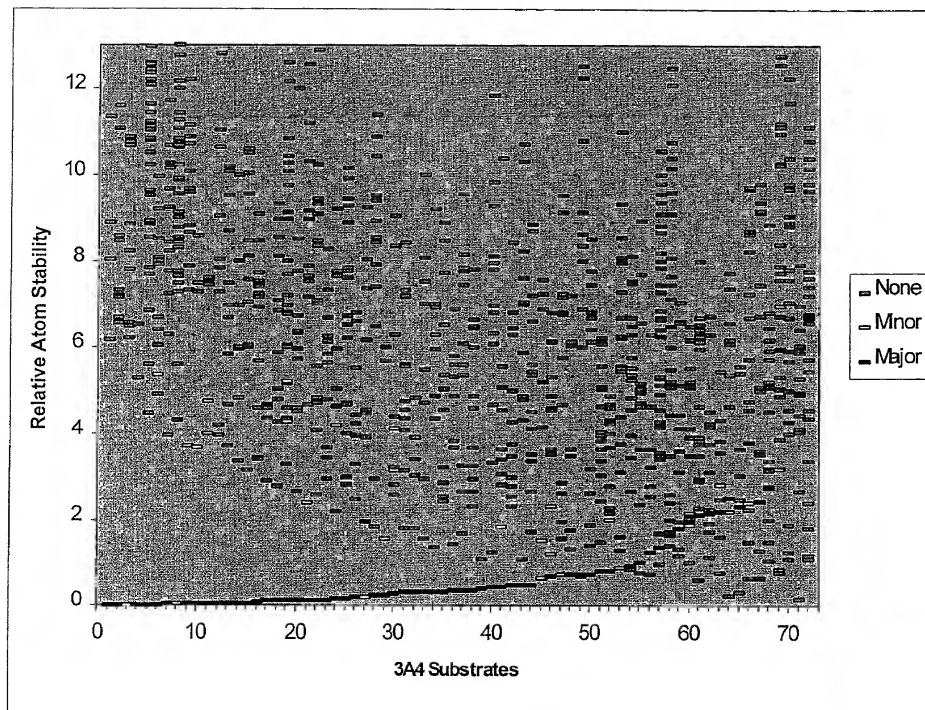
FIGURE 17

Figure 18A

Figure 18B

1902 Client Site at Drug Discovery Site

1908 organic molecule identities

1910 predicted ADME/PK properties

1904 Internet

1908 organic molecule identities

1910 predicted ADME/PK properties

1906 Server

1912 Model

1900

FIGURE 19